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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/715,229 | 11/17/2003 | Tariq M. Rana | UMY-041RCE | 5733 |

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| EXAMINER | |
|---|---|
| CHONG, KIMBERLY | |
| **ART UNIT** | **PAPER NUMBER** |
| 1635 | |
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| 12/11/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/715,229 | RANA, TARIQ M. | |
| | Examiner | Art Unit | |
| | Kimberly Chong | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *2-34* is/are pending in the application.

4a) Of the above claim(s) *18-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Application/Amendment/Claims*

Applicant's response filed 10/02/2007 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 04/02/2007 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 10/02/2007, claims 2-34 are pending in the application. Claims 2-17 are currently under examination.

### *Response to Applicant's Arguments*

### *Re: Claim Rejections - 35 USC § 103*

The rejection of claims 2-8 and 10-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ecker et al. (US Patent No. 5,965,722), Hojo et al. (Eur Respir J, 1998), Hammond et al. (Nature Reviews Genetics, 2001), Bass et al (Nature, 2001) and Tuschl et al. (cited on PTO Form 892 filed 11/15/2005) is maintained for the reasons of record in the Office action mailed 04/02/2007.

Applicant's arguments filed 10/02/2007 have been fully considered but they are not persuasive. Applicant argues the teachings of Ecker et al. are directed to antisense DNA oligonucleotides for specific inhibition of gene expression of a mutant gene and fail

to teach or suggest any RNA oligonucleotide and one would not have been motivated to seek alternate molecules to antisense for specific mutant gene silencing. Applicants further argue that Ecker et al. teach away from the claimed invention because Ecker et al. teach that an RNA oligonucleotide would fail to activate RNase H and thus fail to inhibit expression of target RNA efficiently.

In response to Applicant's argument that one would not have been motivated to seek alternate molecules to antisense for specific gene, Ecker et al. teach a method of inhibiting a mutant gene using an inhibitory antisense nucleic acid molecule and given that both Hammond et al. and Bass et al. teach antisense compounds are less specific compared to siRNA for silencing gene expression, one of skill in the art would have clearly substituted siRNA inhibitory molecules for antisense molecules and would have clearly substituted siRNA molecules for antisense molecules as taught by Ecker et al. to silence mutant gene expression. Further, Applicant's argument that one of skill in the art would not use an RNA oligonucleotide because an RNA would fail to active RNAse H is not convincing because whether or not the siRNA would activate RNase H is irrelevant to the overall motivation to inhibit gene expression. Ecker et al. teach an inhibitory antisense compound with a modified base opposite the mutated code which has complementary to a mutant target gene and teach this antisense compound specifically binds to a mutant target gene and inhibits gene expression. One of skill in the art would have been motivated to substitute the antisense compound taught by Ecker et al. with a more efficient inhibitory molecule for the sole purpose of targeting a mutant gene more efficiently and silencing gene expression of said mutant target gene

more efficiently. Moreover, given that both the antisense compound and siRNA compound are designed to recognize a target gene thru complementary to the target gene, of skill in the art would be motivated to design an siRNA to a mutant target gene and have a reasonable expectation of success at being able to initiate gene silencing of a mutant target gene using a siRNA.

Applicant argues the teachings of Hammond et al. and Bass et al. fail to make up for the deficiencies in Ecker et al. because these references do not teach or suggest siRNA comprising any modified nucleotides and further argues Tuschl et al. do not teach siRNA comprising modifications wherein the modified bases are at any position that is useful for enhancing binding interactions between the siRNA and the mRNA. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir.1986).

Hammond et al. and Bass et al. were relied upon to provide motivation to use a siRNA to inhibit gene expression compared to an antisense compound and were not relied upon to teach modifications of siRNA. Further, Tuschl et al. was relied upon to teach generally siRNA can be made to target any gene and silence gene expression. Therefore one of skill in the art would be motivated to substitute a siRNA for an antisense given that siRNA have proven to be more target specific and one of skill in the art would have been motivated to incorporate a modified base to specifically target a mutant target gene as taught by Ecker et al.

Lastly, Applicant argues one of skill in the art would not have had a reasonable expectation of success in using a siRNA to target a mutant allele because antisense and siRNA molecules operate thru very different cellular mechanisms. Applicant states that it was recognized in the art that siRNAs containing a single base mismatch with the target RNA could effectively mediate RNAi silencing of the target gene and unlike the single nucleotide discrimination obtained with an antisense oligonucleotide, siRNAs are incapable of such single nucleotide discrimination between the wild type and mutant allele.

Applicant's argument regarding the incapability of siRNA to recognize and silence gene expression of mutant genes is not convincing. Applicant has not provided any evidence to the contrary supporting their conclusion that siRNA are incapable of allele specific silencing and are invited to do so and further Applicant contradicts this statement by acknowledging that siRNA are in fact capable of allele-specific gene silencing of a mutant gene relative to wild type gene (see Remarks page 18, first paragraph). As evidenced by Xu et al. (cited in the Office action filed 04/02/2007 and discussed herein), siRNA are capable of allele specific gene silencing wherein the siRNA can selectively inhibit a mutant gene while preserving the expression of the wild-type gene. Xu et al. teach an effective method of using siRNA to treat genetic disorders associated with expression of gain of function proteins from a mutant gene. Thus, one of skill in the art would have clearly had a reasonable expectation of success at generating a siRNA to targeted to a mutant gene and clearly would have expected to be

able to silence gene expression of a mutant target gene given Xu et al. specifically teach allele-specific targeting using a siRNA.

Thus, for the reasons of record and stated above, the rejection is maintained.

The rejection of claims 2-5, 7 and 9-17 under 35 U.S.C. 103(a) as being unpatentable over Ecker et al. (US Patent No. 5,965,722), Hammond et al. (Nature Review Genetics, 2001), Bass et al (Nature, 2001) and Tuschl et al. (cited on PTO Form 892 filed 11/15/2005) and Xu et al. (cited on PTO Form 892 filed 11/15/2005) is maintained for the reasons of record in the Office action mailed 04/02/2007.

Applicant's arguments filed 10/02/2007 have been fully considered but they are not persuasive. Applicant relies on arguments above in the previous 103 rejection for references Ecker et al., Hammond et al., Bass et al., and Tuschl et al. Response to Applicant's arguments is as stated above.

Applicant further argues that while Xu et al. teach allele- specific targeting of a mutant gene while not targeting the wild-type gene, Xu et al. fails to teach an siRNA comprising a modified base position opposite a point mutation in a mutant allele as required by the pending claims. This argument is not convincing. As recited in the previous Office action filed 04/02/07 and reiterated here, Ecker et al. teach antisense oligonucleotides comprising modified nucleotide bases increase the affinity for base mismatches in mutated genes and further enhance the compounds selectivity for such mutated genes and therefore one of skill in the art would have been motivated to incorporate a modified base into a siRNA to enhance the selectivity for mutated genes

such as a Ras gene. Xu et al. was not relied upon to teach incorporation of a modified base opposite a point mutation but was relied upon to teach siRNA are capable of single point discrimination and capable of silencing gene expression of a mutant target gene while not silencing expression of the corresponding wild-type gene.

Thus, for the reasons of record and stated above, the rejection is maintained.

***Re: Claim Rejections - 35 USC § 112***

The rejection of claims 3-17 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in response to Applicant's arguments filed 10/02/2007.

***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Thursday between 6 and 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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KC
Art Unit 1635

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